Human papillomavirus (HPV)

Disease Issues

How common is human papillomavirus (HPV) infection?
HPV is the most common sexually transmitted infection in the United States. In the United States, an estimated 79 million persons are infected, and an estimated 14 million new HPV infections occur every year among persons age 15 through 59 years. Approximately half of new infections occur among persons age 15 through 24 years. First HPV infection occurs within a few months to years of becoming sexually active.

How serious is disease caused by HPV?
HPV is associated with cervical, vulvar, and vaginal cancer in females, penile cancer in males, and anal and oropharyngeal cancer in both females and males. An annual average of approximately 26,900 new cancers were attributable to HPV during 2006 through 2010 including 17,600 (65%) among females and 9,300 (35%) among males. Cervical and oropharyngeal cancers were the most common with an estimated 10,400 cervical cancers and 9,000 oropharyngeal cancers (7,200 among men and 1,800 among women). HPV also causes almost all cases of genital warts.

Which types of HPV are most likely to cause disease?
Of the annual average of 26,900 HPV-related cancers in the United States, approximately 64% are attributable to HPV 16 or 18 (65% for females; 63% for males; approximately 21,300 cases annually), which are included in all three HPV vaccines. Approximately 10% are attributable to HPV types 31, 33, 45, 52, and 58 (14% for females; 4% for males; approximately 3,400 cases annually), which are included in the 9-valent HPV vaccine. HPV type 16, 18, 31, 33, 45, 52, or 58 account for about 81% of cervical cancers in the United States.

Approximately 50% of cervical precancers (CIN2 or greater) are caused by HPV 16 or 18 and 25% by HPV 31, 33, 45, 52, or 58. HPV 6 or 11 cause 90% of anogenital warts (condylomata) and most cases of recurrent respiratory papillomatosis.

More information about HPV and HPV-related cancers is available in the 2014 HPV ACIP statement at www.cdc.gov/mmwr/pdf/rr/rr6305.pdf

Is there a treatment for HPV infection?
There is no treatment for HPV infection. Only HPV-associated lesions including genital warts, recurrent respiratory papillomatosis, precancers, and cancers are treated. Recommended treatments vary depending on the diagnosis, size, and location of the lesion. Local treatment of lesions might not eradicate all HPV containing cells fully; whether available therapies for HPV-associated lesions reduce infectiousness is unclear.

Are healthcare personnel at risk of occupational infection with HPV?
Occupational infection with HPV is possible. Some HPV-associated conditions (including anogenital and oral warts, anogenital intraepithelial neoplasias, and recurrent respiratory papillomatosis) are treated with laser or electrosurgical procedures that could produce airborne particles. These procedures should be performed in an appropriately ventilated room using standard precautions and local exhaust ventilation. Workers in HPV research laboratories who handle wild-type virus or "quasi virions" might be at risk of acquiring HPV from occupational exposures. In the laboratory setting, proper infection control should be instituted including, at minimum, biosafety level 2. Whether HPV vaccination would be of benefit in these settings is unclear because no data exist on transmission risk or vaccine efficacy in this situation.
Can human papillomavirus (HPV) be transmitted by non-sexual transmission routes, such as clothing, undergarments, sex toys, or surfaces?
Nonsexual HPV transmission is theoretically possible but has not been definitely demonstrated. This is mainly because HPV can't be cultured and DNA detection from the environment is difficult and likely prone to false negative results.

Vaccine Recommendations

Please provide more information about the three HPV vaccines, Cervarix (GSK), Gardasil (Merck), and Gardasil 9 (Merck). How do they differ?

- Cervarix (2vHPV, GlaxoSmithKline) is an inactivated bivalent vaccine that protects against HPV types 16 and 18. 2vHPV is licensed for females age 9 through 25 years.
- Gardasil (4vHPV, Merck) is an inactivated quadrivalent vaccine that protects against HPV types 16 and 18, and also against types 6 and 11, which cause genital warts and recurrent respiratory papillomatosis. 4vHPV is licensed for females and males age 9 through 26 years.
- Gardasil 9 (9vHPV, Merck) is an inactivated 9-valent vaccine that contains the 4 virus types included in 4vHPV and 5 additional oncogenic (cancer-causing) HPV types (31, 33, 45, 52 and 58). The 9vHPV vaccine is licensed for females and males age 9 through 26 years.

9vHPV was licensed by the FDA in December 2014 and will eventually replace 4vHPV. However, both vaccines will be available in the United States at least through mid-2016.
9vHPV has the same schedule as 4vHPV (three intramuscular doses spaced 0, 1, and 6 months apart). In a clinical trial comparing 9vHPV to 4vHPV, 9vHPV reduced the risk of disease caused by the 5 additional strains by 97%.

With the availability of 9vHPV, has the ACIP changed its recommendations for HPV vaccines?
The ACIP recommendations for HPV vaccination have not changed. ACIP recommends that routine HPV vaccination be initiated for females and males at age 11 or 12 years. The vaccination series can be started as early as age 9 years. Vaccination is also recommended for females aged 13 through 26 years and for males aged 13 through 21 years who have not been vaccinated previously or who have not completed the 3-dose series. In addition, vaccination is recommended for men age 22 through 26 years who 1) have sex with men or 2) are immunocompromised as a result of infection (including HIV), disease, or medication. Other males 22 through 26 years of age may be vaccinated at the clinician's discretion.
Vaccination of females is recommended with 2vHPV, 4vHPV (as long as this formulation is available), or 9vHPV. Vaccination of males is recommended with 4vHPV (as long as this formulation is available) or 9vHPV. Ideally, HPV vaccine should be administered before potential exposure to HPV through sexual contact.
All three HPV vaccines should be given as a 3-dose schedule, with the second dose given 1 to 2 months after the first dose and the third dose 6 months after the first dose. The minimum interval between the first and second doses of vaccine is 4 weeks. The minimum interval between the second and third doses of vaccine is 12 weeks. The minimum interval between the first and third doses is 24 weeks. If the vaccination series is interrupted the series does not need to be restarted.
The 2014 ACIP recommendations are available at www.cdc.gov/mmwr/pdf/rr/rr6305.pdf (covers 2vHPV and 4vHPV) and the newly released 2015 ACIP recommendations (published March 27, 2015) are at www.cdc.gov/mmwr/pdf/wk/mm6411.pdf, pages 300–304 (covers 9vHPV).

Some parents resist HPV vaccination of their 11- and 12-year-olds because they are not sexually active. How should I counter this position?
Explain to the parent that vaccination starting at 11 or 12 years will provide the best protection possible long before the start of any kind of sexual activity. It is standard practice to vaccinate people before they are exposed to an infection, as is the case with measles and the other recommended childhood vaccines. Similarly, we want to vaccinate children before they get exposed to HPV. Studies of HPV vaccine indicate that younger adolescents respond better to the vaccine than older adolescents and young adults. Finally, there is no evidence that receipt of HPV vaccine increases the chance that a child will become sexually active.

My office recently changed HPV vaccine brands from Gardasil (4vHPV) to Cervarix (2vHPV). We
have several males who received doses of 2vHPV instead of 4vHPV. Do the males who received 2vHPV need to be revaccinated?
Yes. Cervarix (2vHPV, GlaxoSmithKline) is not approved or recommended for use in males. Doses of 2vHPV administered to males should not be counted and need to be repeated using 4vHPV (as long as this formulation is available) or 9vHPV (Gardasil 9, Merck).

If a vaccination series was started with 2vHPV or 4vHPV, can it be completed with 9vHPV? If the answer is yes, what are the spacing intervals that should be used for the remaining doses in the 3-dose series?
ACIP recommendations state that 9vHPV may be used to continue or complete a series started with a different HPV vaccine product. The intervals between doses remain the same regardless of what vaccine is used to complete the series. The second dose is given 1 to 2 months after the first dose and the third dose 4 months after the second AND at least 6 months after the first dose.

Are additional 9vHPV doses recommended for a person who started a series with 2vHPV or 4vHPV and completed the series with one or two doses of 9vHPV?
There is no ACIP recommendation for additional doses of 9vHPV for persons who started the series with 2vHPV or 4vHPV and completed the series with 9vHPV.

Does ACIP recommend revaccination with 9vHPV for patients who previously received a series of 2vHPV or 4vHPV?
ACIP has not recommended routine revaccination with 9vHPV for persons who have completed a series of another HPV vaccine. There are data that indicate revaccination with 9vHPV after a series of 4vHPV is safe. Clinicians should decide if the benefit of immunity against 5 additional oncogenic strains of HPV is justified for their patients.

Is use of HPV vaccine covered under the Vaccines For Children (VFC) program?
Yes.

Are pap smears still necessary for women who receive HPV vaccine?
Yes. Vaccinated women still need to see their healthcare provider for periodic cervical cancer screening. The vaccine does not provide protection against all types of HPV that cause cervical cancer, so even vaccinated women will still be at risk for some cancers from HPV.

Do women and men whose sexual orientation is same-sex need HPV vaccine?
Yes. HPV vaccine is recommended for females and males regardless of their sexual orientation.

Will patients who have already had genital warts benefit from receiving 4vHPV or 9vHPV?
A history of genital warts or clinically evident genital warts indicates infection with HPV, most often type 6 or 11. However, people with this history might not have been infected with both HPV 6 and 11 or with the other HPV types included in 4vHPV and 9vHPV. Vaccination will provide protection against infection with HPV vaccine types the patient has not already acquired. Both 4vHPV and 9vHPV protect against HPV types 6 and 11, which cause 90% of genital warts. 2vHPV does not protect against HPV types that cause genital warts. Providers should advise their patients/clients that the vaccine will not have a therapeutic effect on existing HPV infection or genital warts. It is important, however, that patients receive all 3 doses of 4vHPV or 9vHPV vaccine to get full protection from genital warts.

If a patient has been sexually active for a number of years, is it still recommended to give HPV vaccine or to complete the HPV vaccine series?
Yes. HPV vaccine should be administered to people who are already sexually active. Ideally, patients should be vaccinated before onset of sexual activity; however, patients who have already been infected with one or more HPV types still be protected from other HPV types in the vaccine that have not been acquired.

I read that HPV vaccination rates are still low. What can we do as providers to improve these rates?
Coverage levels for HPV vaccine are improving but are still inadequate. Results from the Centers for Disease Control and Prevention's 2013 National Immunization Survey-Teen (NIS-Teen) indicate that HPV vaccination rates in girls age 13 through 17 years increased between 2012 and 2013. Just over 57% of girls age 13 through 17 years had started the series that they should have completed by age 13 years and 38% had completed the series. In 2013 35% of boys age 13 through 17 years had received one dose but only 14% had received all three recommended doses. A summary of the 2013 NIS-Teen survey is available at www.cdc.gov/mmwr/pdf/wk/mm6329.pdf, pages 625–633.

Providers can improve uptake of this life-saving vaccine in two main ways. First, studies have shown that missed opportunities are a big problem. Up to 88% (depending on year of birth) of girls unvaccinated for HPV had a healthcare visit where they received another vaccine such as Tdap, but not HPV. If HPV vaccine had been administered at the same visit, vaccination coverage for one or more doses could be 91% instead of 57%. Second, the 2013 NIS-Teen data show that not receiving a healthcare provider's recommendation for HPV vaccine was one of the five main reasons parents reported for not vaccinating their daughters and the number one reason for not vaccinating their sons.

CDC urges healthcare providers to increase the consistency and strength of how they recommend HPV vaccine, especially when patients are age 11 or 12 years. The following resources can help providers with these conversations.


For more detailed information about HPV vaccination strategies for providers, visit www.cdc.gov/vaccines/who/teens/for-hcp/hpv-resources.html.

Scheduling and Administering Vaccines

**What is the recommended schedule for administering HPV vaccine?**

All three HPV vaccines should be administered in a 3-dose schedule, with the second dose administered 1 to 2 months after the first dose and the third dose 6 months after the first dose. The minimum interval between the first and second doses of vaccine is 4 weeks. The minimum interval between the second and third doses of vaccine is 12 weeks. The minimum interval between the first and third doses is 24 weeks.

**If a dose of HPV vaccine is significantly delayed, do I need to start the series over?**

No, do not restart the series. You should continue where the patient left off and complete the series.

**To accelerate completion of the HPV vaccine series, can doses be given at 0, 1, and 4 months?**

No, there is no accelerated schedule for completing the HPV vaccine series. You should follow the recommended schedule of 0, 1-2, and 6 months.

**What are the minimum intervals between doses of HPV vaccine?**

Minimum intervals are used when patients have fallen behind on their vaccination schedule or when they need their dosing schedule expedited (for example if there is imminent travel). The minimum interval between the first and second doses of HPV vaccine is 4 weeks. The minimum interval between the second and third dose is 12 weeks. ACIP recommends an interval of 24 weeks between the first and third dose. However, the third dose can be considered to be valid if it was separated from the first dose by at least 16 weeks and from the second dose by at least 12 weeks.

**I work with university students and many of them miss coming in on time for their next dose of HPV vaccine. What's the longest interval allowed before we need to start the series over?**

No vaccine series needs to be restarted because of an interval that is longer than recommended (with the exception of oral typhoid vaccine in certain circumstances). You should continue the series where it was interrupted. If the HPV series is begun when the university student is age 26 or younger, it can be completed after the student turns 27.

**Is it recommended that patients age 26 years start the HPV vaccination series even though they...**
will be older than 26 when they complete it?
Yes. HPV vaccine is recommended for all women through age 26 years and also may be given to men through that age. So, the 3-dose series can be started at age 26 even if it will not be completed at age 26. The series should be completed regardless of the age of the patient (i.e., even if the patient is older than 26). In certain situations, some clinicians choose to start the 3-dose HPV series in patients who are older than 26 years. This, however, is an off-label use.

We inadvertently gave HPV vaccine to a woman who didn't know she was pregnant at the time. How should we complete the schedule?
GlaxoSmithKline and Merck (for 4vHPV) have closed their formal pregnancy registries with the concurrence of the FDA (see next question). However, Merck has established a registry for women who inadvertently receive 9vHPV during pregnancy (telephone 800-986-8999). You should withhold further HPV vaccine until she is no longer pregnant. After the pregnancy is completed, administer the remaining doses of the series using the usual schedule. HPV#2 assuming 1-2 months have passed since HPV#1. Give HPV#3 6 months after HPV#1, but no earlier than 12 weeks after HPV#2.

Why did GlaxoSmithKline and Merck discontinue their registry for collecting reports of pregnant women who inadvertently received HPV vaccine during pregnancy?
Because HPV vaccine is not recommended for use during pregnancy, both companies facilitated a registry to document outcomes when HPV vaccine was inadvertently administered to pregnant women. These registries collected information for more than 6 years, and both companies fulfilled their FDA obligations to facilitate it. The data from the registries are reassuring with respect to safety after pregnancy exposures. Review of the registry data does not support a causal relationship between HPV vaccine and birth defects or other adverse outcomes of pregnancy.

Can HPV vaccine be administered at the same time as other vaccines?
Yes, administration of a different inactivated or live vaccine, either at the same visit or at any time before or after HPV vaccine, is acceptable because HPV is not a live vaccine.

If HPV vaccine is given subcutaneously instead of intramuscularly, does the dose need to be repeated?
Yes. No data exist on the efficacy or safety of HPV vaccine given by the subcutaneous route. All data on efficacy and duration of protection are based on a 3-dose series given on the approved schedule and administered by the intramuscular route. In the absence of data on subcutaneous administration, CDC and the manufacturers recommend that a dose of HPV vaccine given by any route other than intramuscular should be repeated. There is no minimum interval between the invalid (subcutaneous) dose and the repeat dose.

If a 30-year-old female patient insists that she wants to receive HPV vaccine, can I give it to her?
HPV vaccine is not approved for use in women older than age 26 years. Studies have shown that the vaccine is safe in women age 27 years and older. ACIP does not recommend the use of this vaccine outside the FDA licensing guidelines unless the series was started but not completed by age 26 years. Clinicians may choose to administer HPV vaccine off-label to men and women age 27 years or older and should decide if the benefit of the vaccine outweighs the hypothetical risk.

Contraindications and Precautions

What are the contraindications and precautions to HPV vaccine?
Contraindications are the following:
- History of a severe (anaphylactic) reaction to a vaccine component or following a previous dose.
- Pregnancy

The only precaution to HPV vaccine is a moderate or severe acute illness with or without fever. Vaccination should be deferred until the condition improves.
If a woman has had HPV infection, can she still be vaccinated?
Yes. Women who have evidence of present or past HPV infection and who are younger than age 27 years should be vaccinated. They should be advised that the vaccine will not have a therapeutic effect on existing HPV infection or cervical lesions.

Can a woman who is breastfeeding receive HPV vaccine?
Yes.

Is the history of an abnormal pap a contraindication to the HPV vaccine series?
No. Even a woman found to be infected with a strain of HPV that is present in the vaccine could receive protection from the other strains in the vaccine.

Vaccine Safety

What adverse events can be expected following HPV vaccine?
In clinical trials involving more than 35,000 subjects, the most common adverse event was injection site pain, which was reported in 58% to 90% of recipients (depending on vaccine and dose number). Other local reactions, such as redness and/or swelling, were reported in 30% to 40% of recipients. Local reactions were reported more frequently among 9vHPV recipients than among 4vHPV recipients, probably because of the larger amount of aluminum adjuvant present in 9vHPV. Systemic reactions, such as fever, headache, and fatigue, were reported by 2% to 50% of recipients (depending on vaccine and dose number). These symptoms generally occurred at about the same rate in vaccine and placebo recipients.

We've heard stories in the media lately about severe reactions to the HPV vaccine. Is there any substance to these stories?
No. As of March 2014 more than 67 million doses of HPV vaccine have been distributed in the United States. The federal Vaccine Adverse Events Reporting System (VAERS) has received about 25,000 reports of adverse events following HPV vaccination. Of these, more than 92% were classified as nonserious, such as injection site reactions. Although deaths have been reported among vaccine recipients none has been conclusively shown to have been caused by the vaccine. Occurrences of rare conditions, such as Guillain-Barre Syndrome (GBS) have also been reported among vaccine recipients but there is no evidence that HPV vaccine increased the rate of GBS above what is expected in the population.

CDC, working with the FDA and other immunization partners, will continue to monitor the safety of HPV vaccines. You can find complete information on this and other vaccine safety issues at www.cdc.gov/vaccinesafety/Vaccines/HPV/Index.html.

Do HPV vaccines cause fainting?
Nearly all vaccines have been reported to be associated with the fainting (syncope). Post-vaccination syncope has been most frequently reported after three vaccines commonly given to adolescents (HPV, MCV4, and Tdap). However, it is not known whether the vaccines are responsible for post-vaccination syncope or if the association with these vaccines simply reflects the fact that adolescents are generally more likely to experience syncope.

Syncope can cause serious injury. Falls that occur due to syncope after vaccination can be prevented by having the vaccinated person seated or lying down. The person should be observed for 15 minutes following vaccination.